



Clinical trial results:

Metformin treatment vs a diabetes model of antenatal care in women with mild fasting hyperglycaemia diagnosed in pregnancy: a pilot study

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2013-004065-13 |
| Trial protocol | GB |
| Global end of trial date | 04 January 2017 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 02 May 2020 |
| First version publication date | 02 May 2020 |

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | Metform02 |
|-----------------------|-----------|

Additional study identifiers

| | |
|------------------------------------|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Manchester University NHS Foundation Trust |
| Sponsor organisation address | Oxford Road, Manchester, United Kingdom, M13 9WL |
| Public contact | Dr Lynne Webster, Manchester University NHS Foundation Trust, +44 01612764125, research.sponsor@mft.nhs.uk |
| Scientific contact | Dr Lynne Webster, Manchester University NHS Foundation Trust, +44 01612764125, research.sponsor@mft.nhs.uk |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|-----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 04 January 2017 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 04 January 2017 |
| Global end of trial reached? | Yes |
| Global end of trial date | 04 January 2017 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

This study aims to assess the acceptability and feasibility of using a simple treatment with tablets (metformin) for women with mild gestational diabetes. Metformin is safe in pregnancy and has the advantage that frequent blood glucose monitoring is not necessary. We hope this treatment will be effective in reducing the number of babies which gain excessive weight in pregnancy, without the need for frequent hospital visits and high intervention rates which are associated with the intensive antenatal care routinely offered to women with gestational diabetes.

Protection of trial subjects:

Metformin is associated with a number of gastrointestinal side effects and women unable to tolerate the drug will be advised to discontinue (<5% from previous studies). Although metformin treatment aims to reduce blood glucose levels before and after eating, serious hypoglycaemia is very uncommon and metformin is prescribed in several settings without regular blood glucose monitoring. Women randomised to the diabetic antenatal care arm of the study will be asked to perform regular blood glucose monitoring (BGM). This is an onerous task for women in pregnancy but is standard practice within diabetic antenatal clinics. Women who have HBGM outside the target range will be prescribed metformin and those who do not meet target control with metformin will be prescribed adjuvant insulin. This prescribing regime will be in line with current prescribing practices within our hospital. Women in this arm of the study will also be offered monthly ultrasound scans to assess fetal growth. It is usual practice to offer induction of labour to women with a macrosomic fetus (>95th centile) and therefore some women in this group will be offered additional obstetric interventions. Metformin can sometimes cause some stomach upset (sickness and diarrhoea) so the dose will be increased slowly to minimise this side effect. Metformin can also cause taste disturbance and affect appetite. There is a very rare (<1/10,000), but serious side effect of metformin called 'lactic acidosis'. This occurs in individuals with kidney or liver problems. We will perform a blood test at the beginning of the study to ensure that you do not have any liver or kidney problems before you start the metformin tablets to ensure that the treatment is safe for you. Other very rare side effects include skin rashes.

Background therapy:

Standard diabetes antenatal care (NICE diabetes guidelines) with HBGM and scan surveillance.

Evidence for comparator:

The pregnancy outcomes for all women, delivered at St Mary's Hospital Manchester in 2010, who had an oral glucose tolerance test (OGTT) which would fit the proposed IADPSG diagnostic criteria, have recently been reviewed. 4% of all women who had an OGTT had isolated mild fasting hyperglycaemia (fasting 5.1-5.4 mmol/L; 2 hour <8.5mmol/L). All of these women were managed in normal antenatal clinics with no treatment. The frequency of large for gestational age babies (LGA) in this group (defined as >95th centile using centiles adjusted for maternal characteristics, fetal gender and gestation) was 16.4% (95% CI 9.0-27.8%), more than three times the expected frequency. In addition, we have analysed the Manchester data collected as part the HAPO study (n=2388). In this cohort, 201 women (8%) had a fasting blood glucose level between 5.1 and 5.4 mmol/L (normal 2 hour; <8.5mmol/L). The frequency of LGA (>95th centile) in this group was 9.0% compared to 3.9% (p=0.002) in the normoglycaemic group (n=1886) (OR 2.2 (95% CI 1.4-3.3). This data also suggests that the frequency of macrosomic infants delivered to women with mild degrees of fasting hyperglycaemia in the third trimester is unacceptably high. It is therefore timely to determine whether a simple intervention in this group could reduce the number of macrosomic infants delivered. This pilot study will assess the acceptability of metformin, prescribed in conjunction with routine antenatal care, compared to a standard diabetic model of antenatal care. In the study arm, metformin will be titrated up to the maximum tolerated dose in the absence of home blood glucose monitoring (HBGM). Women in the standard diabetic clinic arm will have their treatment titrated according to HBGM with the addition of insulin where blood glucose levels are out of target, this will allow us to make an assessment of the effectiveness of metformin in this group of women with mild fasting hyperglycaemia.

| | |
|---|------------------|
| Actual start date of recruitment | 02 December 2013 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United Kingdom: 40 |
| Worldwide total number of subjects | 40 |
| EEA total number of subjects | 40 |

Notes:

Subjects enrolled per age group

| | |
|---|----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 40 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Over the course of this study we aim to recruit 60 women.

Pre-assignment

Screening details:

Women with risk factors for GDM (NICE 2008) will be offered an oral glucose tolerance test (OGTT) at 26 weeks gestation as part of their routine antenatal care. Women with mild GDM (Fasting 5.1mmol/l- 5.4 mmol/L; 2-hour <8.5 mmol/l) will be recruited into the study.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|-----------|
| Are arms mutually exclusive? | Yes |
| Arm title | Metformin |

Arm description:

Women randomised to the study arm (Metformin only treatment arm) will be prescribed metformin tablets up to 2000mg from randomisation (26-28 weeks gestation) and will stop once they have delivered their baby.

Women will be asked to start with 500mg metformin (1 tablet, Once Daily) taken with food, increasing on Day 4 by an increment of 500mg per day (in other words to 1 tablet, twice daily). Day 7: a further increment of 500mg per day (in other words to 1 tablet, three times daily). On Day 14, women will increase the evening dose of metformin by a further 500mg. If side effects (largely anticipated to be gastro-intestinal) are experienced, the woman should drop to the previous dose or 500mg metformin (whichever is the greater) and wait for 3 days before increasing the dosage again. The maximum recommended dose is 2000mg daily, taken as three divided doses. The usual starting dose is one tablet 2 or 3 times daily given during or after meals.

| | |
|--|---------------|
| Arm type | Experimental |
| Investigational medicinal product name | Metformin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Women randomised to the study arm (Metformin only treatment arm) will be prescribed metformin tablets up to 2000mg from randomisation (26-28 weeks gestation) and will stop once they have delivered their baby.

Women will be asked to start with 500mg metformin (1 tablet, Once Daily) taken with food, increasing on Day 4 by an increment of 500mg per day (in other words to 1 tablet, twice daily). Day 7: a further increment of 500mg per day (in other words to 1 tablet, three times daily). On Day 14, women will increase the evening dose of metformin by a further 500mg. If side effects (largely anticipated to be gastro-intestinal) are experienced, the woman should drop to the previous dose or 500mg metformin (whichever is the greater) and wait for 3 days before increasing the dosage again. The maximum recommended dose is 2000mg daily, taken as three divided doses. The usual starting dose is one tablet 2 or 3 times daily given during or after meals.

| | |
|------------------|---------------|
| Arm title | Standard care |
|------------------|---------------|

Arm description:

In addition to dietary advice and lifestyle advice, women in the standard care arm will be issued with a HBGM meter and asked to record capillary blood glucose before and 1 hour after meals (x 7/day) with target glucose ranges of fasting <5.5 and 1 hour post prandial <7.8mmol/L. Women will be provided

with a contact telephone number and asked to contact the research midwife if the blood sugars are outside the target range on 3 or more occasions within one week. The handheld maternity records will be updated to inform health care professionals that the woman is participating in the trial and has been randomised to the standard care arm. A baseline ultrasound to assess fetal growth will be performed at study visit 1. Women will be reviewed in the research clinic 2 weeks after their initial appointment.

| | |
|---|---------------|
| Arm type | model of care |
| No investigational medicinal product assigned in this arm | |

| Number of subjects in period 1 | Metformin | Standard care |
|---------------------------------------|-----------|---------------|
| Started | 20 | 20 |
| Completed | 17 | 19 |
| Not completed | 3 | 1 |
| Physician decision | 2 | - |
| Transferred care | 1 | - |
| Discontinued intervention | - | 1 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|-----------|
| Reporting group title | Metformin |
|-----------------------|-----------|

Reporting group description:

Women randomised to the study arm (Metformin only treatment arm) will be prescribed metformin tablets up to 2000mg from randomisation (26-28 weeks gestation) and will stop once they have delivered their baby.

Women will be asked to start with 500mg metformin (1 tablet, Once Daily) taken with food, increasing on Day 4 by an increment of 500mg per day (in other words to 1 tablet, twice daily). Day 7: a further increment of 500mg per day (in other words to 1 tablet, three times daily). On Day 14, women will increase the evening dose of metformin by a further 500mg. If side effects (largely anticipated to be gastro-intestinal) are experienced, the woman should drop to the previous dose or 500mg metformin (whichever is the greater) and wait for 3 days before increasing the dosage again. The maximum recommended dose is 2000mg daily, taken as three divided doses. The usual starting dose is one tablet 2 or 3 times daily given during or after meals.

| | |
|-----------------------|---------------|
| Reporting group title | Standard care |
|-----------------------|---------------|

Reporting group description:

In addition to dietary advice and lifestyle advice, women in the standard care arm will be issued with a HBGM meter and asked to record capillary blood glucose before and 1 hour after meals (x 7/day) with target glucose ranges of fasting <5.5 and 1 hour post prandial <7.8mmol/L. Women will be provided with a contact telephone number and asked to contact the research midwife if the blood sugars are outside the target range on 3 or more occasions within one week. The handheld maternity records will be updated to inform health care professionals that the woman is participating in the trial and has been randomised to the standard care arm. A baseline ultrasound to assess fetal growth will be performed at study visit 1. Women will be reviewed in the research clinic 2 weeks after their initial appointment.

| Reporting group values | Metformin | Standard care | Total |
|------------------------------|-----------|---------------|-------|
| Number of subjects | 20 | 20 | 40 |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 20 | 20 | 40 |
| Age continuous | | | |
| Units: years | | | |
| median | 31 | 33 | |
| inter-quartile range (Q1-Q3) | 26 to 34 | 28 to 35 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 20 | 20 | 40 |
| Male | 0 | 0 | 0 |
| Smokers | | | |
| Units: Subjects | | | |
| Yes | 1 | 0 | 1 |
| No | 19 | 20 | 39 |
| Ethnicity | | | |
| Units: Subjects | | | |
| White | 7 | 4 | 11 |
| Black | 4 | 5 | 9 |
| Asian | 6 | 7 | 13 |
| Other | 3 | 4 | 7 |

| | | | |
|--|----------------------|----------------------|---|
| BMI Units: ratio median inter-quartile range (Q1-Q3) | 31 27.5 to 35.0 | 29 25.5 to 34.0 | - |
| Parity Units: Count median inter-quartile range (Q1-Q3) | 1 0 to 2 | 1 0 to 2 | - |
| Fasting glucose at OGTT Units: mmol/L median inter-quartile range (Q1-Q3) | 5.2 5.10 to 5.30 | 5.2 5.15 to 5.35 | - |
| 2H glucose at OGTT Units: mmol/L median inter-quartile range (Q1-Q3) | 6.50 5.55 to 7.05 | 5.95 4.70 to 6.90 | - |
| HbA1c at baseline Units: mmol/L median inter-quartile range (Q1-Q3) | 33.5 30.0 to 35.0 | 32.0 29.0 to 37.0 | - |

End points

End points reporting groups

| | |
|-----------------------|-----------|
| Reporting group title | Metformin |
|-----------------------|-----------|

Reporting group description:

Women randomised to the study arm (Metformin only treatment arm) will be prescribed metformin tablets up to 2000mg from randomisation (26-28 weeks gestation) and will stop once they have delivered their baby.

Women will be asked to start with 500mg metformin (1 tablet, Once Daily) taken with food, increasing on Day 4 by an increment of 500mg per day (in other words to 1 tablet, twice daily). Day 7: a further increment of 500mg per day (in other words to 1 tablet, three times daily). On Day 14, women will increase the evening dose of metformin by a further 500mg. If side effects (largely anticipated to be gastro-intestinal) are experienced, the woman should drop to the previous dose or 500mg metformin (whichever is the greater) and wait for 3 days before increasing the dosage again. The maximum recommended dose is 2000mg daily, taken as three divided doses. The usual starting dose is one tablet 2 or 3 times daily given during or after meals.

| | |
|-----------------------|---------------|
| Reporting group title | Standard care |
|-----------------------|---------------|

Reporting group description:

In addition to dietary advice and lifestyle advice, women in the standard care arm will be issued with a HBGM meter and asked to record capillary blood glucose before and 1 hour after meals (x 7/day) with target glucose ranges of fasting <5.5 and 1 hour post prandial <7.8mmol/L. Women will be provided with a contact telephone number and asked to contact the research midwife if the blood sugars are outside the target range on 3 or more occasions within one week. The handheld maternity records will be updated to inform health care professionals that the woman is participating in the trial and has been randomised to the standard care arm. A baseline ultrasound to assess fetal growth will be performed at study visit 1. Women will be reviewed in the research clinic 2 weeks after their initial appointment.

Primary: Study compliance

| | |
|-----------------|---------------------------------|
| End point title | Study compliance ^[1] |
|-----------------|---------------------------------|

End point description:

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Over study duration

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This is a feasibility study with feasibility outcomes looking at recruitment and acceptability and for this type of endpoint no statistical analysis is required. The first outcome is recruitment. 147 women out of 173 women with OGTT results meeting the study criteria met the inclusion criteria for the trial. Of these women, 40 women (27%) agreed to take part in the study.

| End point values | Metformin | Standard care | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 20 | 20 | | |
| Units: Subjects | 17 | 19 | | |

Statistical analyses

No statistical analyses for this end point

Primary: Intervention compliance with 2g

| | |
|-----------------|---|
| End point title | Intervention compliance with 2g ^[2] ^[3] |
|-----------------|---|

End point description:

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Overall

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This is a feasibility study with feasibility outcomes looking at recruitment and acceptability and for this type of endpoint no statistical analysis is required. The first outcome is recruitment. 147 women out of 173 women with OGTT results meeting the study criteria met the inclusion criteria for the trial. Of these women, 40 women (27%) agreed to take part in the study.

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This is a treatment specific endpoint designed to inform the future study around treatment adherence. Therefore it is not relevant to the control group and there is no equivalent measure.

| End point values | Metformin | | | |
|---------------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 13 | | | |
| Units: Percentage | | | | |
| median (inter-quartile range (Q1-Q3)) | 68 (48 to 85) | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Maximum metformin dose

| | |
|-----------------|--|
| End point title | Maximum metformin dose ^[4] ^[5] |
|-----------------|--|

End point description:

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Whole study

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This is a feasibility study with feasibility outcomes looking at recruitment and acceptability and for this type of endpoint no statistical analysis is required. The first outcome is recruitment. 147 women out of 173 women with OGTT results meeting the study criteria met the inclusion criteria for the trial. Of these women, 40 women (27%) agreed to take part in the study.

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This is a treatment specific endpoint designed to inform the future study around treatment adherence. Therefore it is not relevant to the control group and there is no equivalent measure.

| End point values | Metformin | | | |
|---------------------------------------|---------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 15 | | | |
| Units: mg | | | | |
| median (inter-quartile range (Q1-Q3)) | 2000 (1000 to 2000) | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Happy to participate

| | |
|------------------------|-------------------------------------|
| End point title | Happy to participate ^[6] |
| End point description: | |
| End point type | Primary |
| End point timeframe: | |
| Completion | |

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This is a feasibility study with feasibility outcomes looking at recruitment and acceptability and for this type of endpoint no statistical analysis is required. The first outcome is recruitment. 147 women out of 173 women with OGTT results meeting the study criteria met the inclusion criteria for the trial. Of these women, 40 women (27%) agreed to take part in the study.

| End point values | Metformin | Standard care | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 19 | 17 | | |
| Units: Subjects | | | | |
| Yes | 18 | 17 | | |
| No | 1 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Primary: When you started the study, how did you feel about your allocation?

| | |
|------------------------|--|
| End point title | When you started the study, how did you feel about your allocation? ^[7] |
| End point description: | |
| End point type | Primary |
| End point timeframe: | |
| Duration | |

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This is a feasibility study with feasibility outcomes looking at recruitment and acceptability and for this type of endpoint no statistical analysis is required. The first outcome is recruitment. 147 women out of 173 women with OGTT results meeting the study criteria met the inclusion criteria for the trial. Of these women, 40 women (27%) agreed to take part in the study.

| End point values | Metformin | Standard care | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 18 | 17 | | |
| Units: Subjects | | | | |
| Not satisfied | 0 | 0 | | |
| Satisfied | 15 | 14 | | |
| Not sure | 3 | 2 | | |
| Missing | 0 | 1 | | |

Statistical analyses

No statistical analyses for this end point

Primary: Now you have completed the study, how do you feel about your allocation?

| | |
|-----------------|---|
| End point title | Now you have completed the study, how do you feel about your allocation? ^[8] |
|-----------------|---|

End point description:

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

End of study

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This is a feasibility study with feasibility outcomes looking at recruitment and acceptability and for this type of endpoint no statistical analysis is required. The first outcome is recruitment. 147 women out of 173 women with OGTT results meeting the study criteria met the inclusion criteria for the trial. Of these women, 40 women (27%) agreed to take part in the study.

| End point values | Metformin | Standard care | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 18 | 17 | | |
| Units: Subjects | | | | |
| Not satisfied | 0 | 0 | | |
| Satisfied | 18 | 17 | | |
| Not sure | 0 | 0 | | |
| Missing | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Primary: How do you feel about your antenatal care since you enrolled in the study?

| | |
|-----------------|---|
| End point title | How do you feel about your antenatal care since you enrolled in the study? ^[9] |
|-----------------|---|

End point description:

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Duration

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This is a feasibility study with feasibility outcomes looking at recruitment and acceptability and for this type of endpoint no statistical analysis is required. The first outcome is recruitment. 147 women out of 173 women with OGTT results meeting the study criteria met the inclusion criteria for the trial. Of these women, 40 women (27%) agreed to take part in the study.

| End point values | Metformin | Standard care | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 18 | 17 | | |
| Units: subjects | | | | |
| Not satisfied | 0 | 0 | | |
| Satisfied | 18 | 17 | | |
| Not sure | 0 | 0 | | |
| Missing | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Primary: If the study included a 'no treatment' allocation, would you have still been happy to take part in the study?

| | |
|-----------------|---|
| End point title | If the study included a 'no treatment' allocation, would you have still been happy to take part in the study? ^[10] |
|-----------------|---|

End point description:

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Duration

Notes:

[10] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This is a feasibility study with feasibility outcomes looking at recruitment and acceptability and for this type of endpoint no statistical analysis is required. The first outcome is recruitment. 147 women out of 173 women with OGTT results meeting the study criteria met the inclusion criteria for the trial. Of these women, 40 women (27%) agreed to take part in the study.

| End point values | Metformin | Standard care | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 18 | 17 | | |
| Units: Subjects | | | | |
| Yes | 14 | 16 | | |
| No | 4 | 1 | | |
| Missing | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Primary: How often did you forget to take your medication?

| | |
|-----------------|---|
| End point title | How often did you forget to take your medication? ^[11] |
|-----------------|---|

End point description:

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Duration

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This is a feasibility study with feasibility outcomes looking at recruitment and acceptability and for this type of endpoint no statistical analysis is required. The first outcome is recruitment. 147 women out of 173 women with OGTT results meeting the study criteria met the inclusion criteria for the trial. Of these women, 40 women (27%) agreed to take part in the study.

| End point values | Metformin | Standard care | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 18 | 17 | | |
| Units: Subjects | | | | |
| No medication | 0 | 4 | | |
| Never or rarely | 12 | 8 | | |
| 1-3 times/wk | 5 | 5 | | |
| 4-6 times/wk | 0 | 0 | | |
| >6 times/wk | 1 | 0 | | |
| Missing | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Primary: Which part of your diabetes treatment was easiest?

| | |
|-----------------|--|
| End point title | Which part of your diabetes treatment was easiest? ^[12] |
|-----------------|--|

End point description:

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Duration

Notes:

[12] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This is a feasibility study with feasibility outcomes looking at recruitment and acceptability and for this type of endpoint no statistical analysis is required. The first outcome is recruitment. 147 women out of 173 women with OGTT results meeting the study criteria met the inclusion criteria for the trial. Of these women, 40 women (27%) agreed to take part in the study.

| End point values | Metformin | Standard care | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 18 | 17 | | |
| Units: Subjects | | | | |
| Doing finger-prick tests | 0 | 7 | | |
| Being careful with diet | 1 | 2 | | |
| Taking medication | 16 | 7 | | |
| Missing | 1 | 1 | | |

Statistical analyses

No statistical analyses for this end point

Primary: Which part of your diabetes treatment was hardest?

| | |
|-----------------|--|
| End point title | Which part of your diabetes treatment was hardest? ^[13] |
|-----------------|--|

End point description:

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Duration

Notes:

[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This is a feasibility study with feasibility outcomes looking at recruitment and acceptability and for this type of endpoint no statistical analysis is required. The first outcome is recruitment. 147 women out of 173 women with OGTT results meeting the study criteria met the inclusion criteria for the trial. Of these women, 40 women (27%) agreed to take part in the study.

| End point values | Metformin | Standard care | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 18 | 17 | | |
| Units: Subjects | | | | |
| Doing finger-prick tests | 0 | 7 | | |
| Being careful with diet | 12 | 9 | | |
| Taking medication | 4 | 0 | | |
| Missing | 2 | 1 | | |

Statistical analyses

No statistical analyses for this end point

Primary: In future pregnancy, if you developed diabetes again, would you choose?

| | |
|-----------------|---|
| End point title | In future pregnancy, if you developed diabetes again, would you choose? ^[14] |
|-----------------|---|

End point description:

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Duration

Notes:

[14] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This is a feasibility study with feasibility outcomes looking at recruitment and acceptability and for this type of endpoint no statistical analysis is required. The first outcome is recruitment. 147 women out of 173 women with OGTT results meeting the study criteria met the inclusion criteria for the trial. Of these women, 40 women (27%) agreed to take part in the study.

| End point values | Metformin | Standard care | | |
|--|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 18 | 17 | | |
| Units: Subjects | | | | |
| Monitoring in a diabetic antenatal clinic | 8 | 15 | | |
| Metformin, no home blood glucose / hospital visits | 9 | 0 | | |
| No treatment at all | 1 | 1 | | |
| Missing | 0 | 1 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: HbA1C at 36-38 weeks

| | |
|-----------------|----------------------|
| End point title | HbA1C at 36-38 weeks |
|-----------------|----------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

36-38 weeks

| End point values | Metformin | Standard care | | |
|---------------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 20 | 20 | | |
| Units: mmol/L | | | | |
| median (inter-quartile range (Q1-Q3)) | 35.5 (31.0 to 40.0) | 37.0 (35.0 to 41.0) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of "none diabetes" scans

| | |
|-----------------|---------------------------------|
| End point title | Number of "none diabetes" scans |
|-----------------|---------------------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Secondary

| End point values | Metformin | Standard care | | |
|---------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 20 | 20 | | |
| Units: Range | | | | |
| median (inter-quartile range (Q1-Q3)) | 3 (2 to 5) | 5 (0 to 9) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of clinic attendances post randomisation

| | |
|-----------------|---|
| End point title | Number of clinic attendances post randomisation |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Duration

| End point values | Metformin | Standard care | | |
|---------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 20 | 20 | | |
| Units: Range | | | | |
| median (inter-quartile range (Q1-Q3)) | 2.5 (2 to 5) | 7 (4 to 9) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of phone calls

| | |
|-----------------|-----------------------|
| End point title | Number of phone calls |
|-----------------|-----------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Duration

| End point values | Metformin | Standard care | | |
|---------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 20 | 20 | | |
| Units: Number | | | | |
| median (inter-quartile range (Q1-Q3)) | 2 (1 to 4) | 2 (0 to 2) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of admissions

| | |
|-----------------|----------------------|
| End point title | Number of admissions |
|-----------------|----------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Duration

| End point values | Metformin | Standard care | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 20 | 20 | | |
| Units: Admissions | 1 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Spontaneous labour onset

| | |
|-----------------|--------------------------|
| End point title | Spontaneous labour onset |
|-----------------|--------------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Labour

| End point values | Metformin | Standard care | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 19 | 20 | | |
| Units: Subjects | 5 | 6 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Delivery - vaginal

| | |
|-----------------|--------------------|
| End point title | Delivery - vaginal |
|-----------------|--------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Labour

| End point values | Metformin | Standard care | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 19 | 20 | | |
| Units: Subjects | 11 | 15 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Gestation at delivery

| | |
|-----------------|-----------------------|
| End point title | Gestation at delivery |
|-----------------|-----------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Delivery

| End point values | Metformin | Standard care | | |
|---------------------------------------|------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 19 | 20 | | |
| Units: Days | | | | |
| median (inter-quartile range (Q1-Q3)) | 278 (270 to 282) | 273 (270 to 276) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: LGA (greater than or equal to 95th centile)

| | |
|-----------------|---|
| End point title | LGA (greater than or equal to 95th centile) |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Birth

| End point values | Metformin | Standard care | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 19 | 20 | | |
| Units: Babies | 1 | 2 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: LGA (greater than or equal to 4000g)

| | |
|------------------------|--------------------------------------|
| End point title | LGA (greater than or equal to 4000g) |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Birth | |

| End point values | Metformin | Standard care | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 19 | 20 | | |
| Units: Babies | 3 | 1 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Centile

| | |
|------------------------|-----------|
| End point title | Centile |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Birth | |

| End point values | Metformin | Standard care | | |
|---------------------------------------|---------------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 19 | 20 | | |
| Units: centile | | | | |
| median (inter-quartile range (Q1-Q3)) | 45.5 (11.7 to 62.1) | 33.95 (11.8 to 48.25) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: NICU admission

| | |
|------------------------|----------------|
| End point title | NICU admission |
| End point description: | |
| End point type | Secondary |

End point timeframe:

After birth

| End point values | Metformin | Standard care | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 19 | 20 | | |
| Units: Babies | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Shoulder dystocia

| | |
|-----------------|-------------------|
| End point title | Shoulder dystocia |
|-----------------|-------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

After birth

| End point values | Metformin | Standard care | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 19 | 20 | | |
| Units: Babies | 1 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The occurrence of adverse events will be sought by non-directive questioning of the patient during the study. Adverse events also may be detected when they are volunteered by the patient.

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|---|
| Dictionary version | 1 |
|--------------------|---|

Reporting groups

| | |
|-----------------------|-----------|
| Reporting group title | Metformin |
|-----------------------|-----------|

Reporting group description:

Women randomised to the study arm (Metformin only treatment arm) will be prescribed metformin tablets up to 2000mg from randomisation (26-28 weeks gestation) and will stop once they have delivered their baby.

Women will be asked to start with 500mg metformin (1 tablet, Once Daily) taken with food, increasing on Day 4 by an increment of 500mg per day (in other words to 1 tablet, twice daily). Day 7: a further increment of 500mg per day (in other words to 1 tablet, three times daily). On Day 14, women will increase the evening dose of metformin by a further 500mg. If side effects (largely anticipated to be gastro-intestinal) are experienced, the woman should drop to the previous dose or 500mg metformin (whichever is the greater) and wait for 3 days before increasing the dosage again. The maximum recommended dose is 2000mg daily, taken as three divided doses. The usual starting dose is one tablet 2 or 3 times daily given during or after meals.

| | |
|-----------------------|---------------|
| Reporting group title | Standard care |
|-----------------------|---------------|

Reporting group description:

In addition to dietary advice and lifestyle advice, women in the standard care arm will be issued with a HBGM meter and asked to record capillary blood glucose before and 1 hour after meals (x 7/day) with target glucose ranges of fasting <5.5 and 1 hour post prandial <7.8mmol/L. Women will be provided with a contact telephone number and asked to contact the research midwife if the blood sugars are outside the target range on 3 or more occasions within one week. The handheld maternity records will be updated to inform health care professionals that the woman is participating in the trial and has been randomised to the standard care arm. A baseline ultrasound to assess fetal growth will be performed at study visit 1. Women will be reviewed in the research clinic 2 weeks after their initial appointment.

| Serious adverse events | Metformin | Standard care | |
|---|----------------|----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 20 (0.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Pregnancy, puerperium and perinatal conditions | | | |
| Shoulder dystocia | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 20 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events | Metformin | Standard care | |
|---|-----------------|----------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 3 / 20 (15.00%) | 1 / 20 (5.00%) | |
| Pregnancy, puerperium and perinatal conditions | | | |
| Baby not moving | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 20 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Reduced fetal movements | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 20 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| General disorders and administration site conditions | | | |
| Generally unwell | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 20 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Vomitting | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 1 / 20 (5.00%) | |
| occurrences (all) | 1 | 1 | |
| Gastrointestinal disorders | | | |
| Abdominal cramps | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 20 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Breathless | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 1 / 20 (5.00%) | |
| occurrences (all) | 1 | 1 | |
| Infections and infestations | | | |
| Urinary Tract Infection | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 20 (0.00%) | |
| occurrences (all) | 1 | 0 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|--------------------------------------|
| 19 October 2014 | SA01 - TBC - need summary of changes |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

| |
|-------|
| None. |
|-------|

Notes: